UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

In re Viagra Products Liability Litigation — Civil No. 06-md-1724

This Order Relates to **ALL ACTIONS** — **MEMORANDUM AND ORDER**

This matter is before the Court on Defendant Pfizer Inc.'s ("Pfizer") Motion to Exclude Plaintiffs' Experts under Daubert, Plaintiffs' Motion to Exclude Defendant's General Causation Experts, and Pfizer's Motion to Strike the March 6, 2008, Affidavit of Gerald McGwin, Jr. For the reasons that follow, the Court grants Pfizer's Daubert Motion in part and denies it in part, denies Plaintiffs' Motion, and denies Pfizer's Motion to Strike.

BACKGROUND

This Multi-District Litigation involves claims that Viagra, manufactured by Pfizer, has caused a vision-loss disorder called non-arteritic anterior ischemic optic neuropathy ("NAION"). It is believed that NAION results from diminished blood flow to the frontal portion of the optic nerve. What causes the diminished blood flow is unclear.

Ten studies have measured Viagra's effect on eye circulation flow but none has measured blood supply to the area believed involved with the disease, apparently because existing medical technology does not permit such a study. (See Pfizer's Supp. Mem. at 9-10; Plaintiffs' Opp'n Mem. at 25.) Although the parties' experts have identified NAION as the most common optic disorder of its type among persons 50 and older, it nevertheless is a rare disorder that afflicts perhaps 2.5 to 11.8 persons per 100,000 in the general population.

Viagra use, by contrast, is anything but rare. Since 1998, when the Food and Drug

Administration approved the drug to treat penile erectile dysfunction ("ED"), it has been prescribed to more than 27 million men. To date the number of Plaintiffs with actions alleging that Viagra has caused their NAION stands at 134—a small number when compared with how many men use Viagra.

Viagra and its active ingredient, sildenafil, work by inhibiting an enzyme called phosphodiesterase type 5 ("PDE5"), thereby causing blood vessels to expand and accordingly improving men's erections. Other PDE5 inhibitors include drugs commonly known as Cialis and Levitra. Three epidemiologic studies have investigated whether there is a link between PDE5 inhibitor use and NAION. None has found a statistically significant increase in NAION among Viagra users. However, because case reports have suggested a possible association between PDE5 inhibitor use and NAION, the FDA in 2005 approved that the label on PDE5 inhibitors read as follows:

> Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA. . . . It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

(Pfizer's Supp. Mem. at 10-11 (citing Leskin Aff. Ex. 33 at 22).) At that time, the FDA also issued the following Alert:

> A small number of men have lost eyesight in one eye some time after taking Viagra, Cialis, or Levitra. This type of vision loss is called non-arteritic anterior ischemic optic neuropathy (NAION). NAION causes a sudden loss of eyesight because blood flow is blocked to the optic nerve.
>
> We do not know at this time if Viagra, Cialis, or Levitra causes NAION.

NAION also happens in men who do not take these medicines.

(Id. at 11 (citing McGwin Dep. Ex. 12).)

Plaintiffs have identified four general-causation experts whose testimony they contend will assist the triers of fact with understanding the evidence and determining that Viagra can cause NAION. See Fed. R. Evid. 702; Ruggiero v. Warner-Lambert Co., 424 F.3d 249, 251 n.1 (2d Cir. 2005) (distinguishing between general causation, which "bears on whether the type of injury at issue can be caused or exacerbated by the defendant's product," and specific causation, which "bears on whether, in the particular instance, the injury actually was caused or exacerbated by the defendant's product"). Pfizer has identified three experts in response.

In these cross-Motions, the parties asked the Court to exclude the testimony pursuant to Rule 702 and the decision in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993). The parties submitted deposition testimony from the experts and numerous exhibits and appeared at a February 12, 2008, hearing. After the hearing, Plaintiffs submitted an affidavit from one of their experts, Gerald McGwin, Jr., in response to the Court's question about what data can be attributed specifically to Viagra as opposed to other PDE5 inhibitors. Pfizer filed a Motion to Strike the affidavit.

DISCUSSION

A. Rule 702 and Daubert Standard

1. In General

Expert opinion testimony from a qualified expert is admissible if "(1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles

and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case." Fed. R. Evid. 702. On a Daubert motion, the Court acts as a gatekeeper to "ensure that any and all scientific testimony . . . is not only relevant, but reliable." Daubert, 509 U.S. at 589.

Factors the Court should examine when determining reliability include whether (1) a theory or technique can be and has been tested, (2) the theory or technique has been subjected to peer review and publication, (3) there is a known or potential rate of error and whether there are standards for controlling the error, and (4) whether the theory or technique enjoys general acceptance within the relevant scientific community. Id. at 592-95. Additional factors include whether (5) the expertise was developed for litigation or naturally flowed from the expert's research, (6) the proposed expert ruled out other alternative explanations, and (7) the proposed expert sufficiently connected the proposed testimony with the facts of the case. Sappington v. Skyjack, Inc., 512 F.3d 440, 449 (8th Cir. 2008).

Expert testimony may be based either on professional studies or personal experience as long as the expert "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 152 (1999). However, to be reliable and therefore admissible, the evidence must provide a "valid . . . connection to the pertinent inquiry." Id. at 149 (quoting Daubert, 509 U.S. 592). "[N]othing in either Daubert or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the ipse dixit of the expert. A court may conclude that there is simply too great an analytical

gap between the data and the opinion offered." Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997).

2. Expert medical testimony

When a case involves expert medical testimony, the Court's function under Daubert is to ensure that the expert's opinion "is scientifically valid and . . . will assist the jury." Glastetter v. Novartis Pharms. Corp., 252 F.3d 986, 988 (8th Cir. 2001) (citing Daubert, 509 U.S. at 589-93). The Court "must make 'a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.'" Id. (quoting Daubert, 509 U.S. at 593-93). "An expert opinion 'must be supported by appropriate validation—i.e., 'good grounds,' based on what is known." Id. at 588-89 (quoting Daubert, 509 U.S. at 590). The goal is to "separate[] expert opinion evidence based on good grounds from subjective speculation that masquerades as scientific knowledge." Id. at 989 (citation and quotation omitted).

The general rule that the "factual basis of an expert opinion goes to the credibility of the testimony, not the admissibility" applies equally to Daubert motions in MDL matters involving allegations that a drug has caused harm to plaintiffs. In re Baycol Prods. Litig., MDL No. 1431, 532 F. Supp. 2d 1029, 1036 (D. Minn. 2007) (Davis, J.) (citing Bonner v. ISP Techs., 259 F.3d 924, 929-30 (8th Cir. 2001)). "Although it is common that medical experts often disagree on diagnosis and causation, questions of conflicting evidence must be left for the jury's determination." Id. "Only if the expert's opinion is so fundamentally

unsupported that it can offer no assistance to the jury must such testimony be excluded." Id. (quoting Bonner, 259 F.3d at 929-30).

Expert opinions in medical-related cases typically involve results from clinical trials, epidemiologic studies, and case studies. The clinical trial is the "gold standard" of medical research. In re Rezulin Prods. Liab. Litig., MDL No. 1348, 369 F. Supp. 2d 398, 406 (S.D.N.Y. 2005) (citing Michael D. Green et al., Reference Guide on Epidemiology, in Reference Manual on Scientific Evidence 333, 338) (Fed. Jud. Ctr. 2d ed. 2000) (hereinafter "Reference Manual")). When research from a clinical trial is unavailable, epidemiologic studies often are used to assess an association between a drug and disease and in turn general causation. Id. at 406 & nn. 55-57.

> Epidemiologic evidence identifies agents that are associated with an increased risk of disease in groups of individuals, quantifies the amount of excess disease that is associated with an agent, and provides a profile of the type of individual who is likely to contract a disease after being exposed to an agent. Epidemiology focuses on the question of general causation (i.e., is the agent capable of causing disease?) rather than that of specific causation (i.e., did it cause a disease in a particular individual?).

Reference Manual at 335-36.

One approach for expressing an association in epidemiologic research is the rate of "relative risk" ("RR"), which is reached by comparing the incidence rate of persons exposed to an agent with the incidence rate of those not exposed. Id. at 348. An RR greater than 1.0 suggests that "[t]here is a positive association between exposure to the agent and the disease, which could be causal." Id. at 349. Courts sometimes conclude that an RR of 2.0 or greater provides reliable evidence of specific causation. Id. at 384 (citing Daubert v. Merrell Dow

Pharms., Inc., 43 F.3d 1311, 1321 (9th Cir. 2001) ("Daubert II") (decision on remand); Manko v. United States, 636 F. Supp. 1419, 1438 (W.D. Mo. 1986), aff'd in part, 830 F.2d 831 (8th Cir. 1987)); but see Miller v. Pfizer, Inc., 196 F. Supp. 2d 1062, 1079 (D. Kan. 2002) ("Court rejects Pfizer's argument that unless Zoloft is shown to create a relative risk [of akathisia] greater than 2.0, [expert's] testimony is inadmissible"), aff'd, 356 F.3d 1326 (10th Cir. 2004), cert. denied, 125 S. Ct. 40 (2004).

Another approach for expressing an association in epidemiologic research is the "odds ratio" ("OR"). "In a case-control study, the odds ratio is the ratio of the odds that a case (one with the disease) was exposed to the odds that a control (one without a disease) was exposed." Reference Manual at 350. Therefore, an OR greater than 1.0 means that a disease is more prevalent in persons who were exposed to a substance than those who were not. The OR is most useful in gauging an association when a disease is "relatively rare" in the general population. Id. at 351. To determine whether an odds ratio provides reliable evidence of causation, courts frequently examine the "confidence interval" ("CI"), or the "range of values within which the true value is likely to fall." Id. at 389. It is generally accepted that "[i]f the confidence interval is so great that it includes the number 1.0, then the study will be said to show no statistically significant association between the factor and the disease." Brock v. Merrill Dow Pharms., Inc., 874 F.2d 307, 312 (5th Cir. 1989).

Besides epidemiologic research, individual case reports containing "a description of a particular patient's clinical history and symptoms" are used to assess an association between a disease and a substance. In re Rezulin Prods. Liab. Litig., 369 F. Supp. 2d at 406.

However, "[c]ase reports lack controls and thus do not provide as much information as controlled epidemiological studies do." Reference Manual at 475. Therefore, case reports are less reliable for establishing causation. In re Rezulin Prods. Liab. Litig., 369 F. Supp. 2d at 406.

B. Plaintiffs' Experts

1. Gerald McGwin, Ph.D.

Plaintiffs' first general-causation expert is Gerald McGwin, Ph.D., an associate professor at the University of Alabama at Birmingham whose research interests include injury epidemiology and ophthalmic epidemiology. In his report and during a deposition, McGwin discussed three epidemiologic studies that, according to McGwin, suggest that Viagra can cause NAION. Two of the studies were published and peer-reviewed. (McGwin Rep. at 2.) One of those studies involved case-control research that McGwin helped perform ("McGwin et al.") and the other involved research of Veterans Administration data ("Margo et al."). A third study ("Gorkin") involved Pfizer-sponsored research.

He examined the studies in light of the so-called "Bradford Hill criteria" that researchers use to assess causation. "The Bradford Hill factors are strength of relationship, consistency, specificity, temporality, dose response, biologic plausibility, coherence, experimental evidence, and analogy." Dunn v. Sandoz Pharms. Corp., 275 F. Supp. 2d 672, 677 n.5 (M.D.N.C. 2003); see also Hollander v. Sandoz Pharm. Corp., 289 F.3d 1193, 1204 n.7 (10th Cir. 2002) (explaining that Bradford Hill factors should be considered "before deciding that the most likely interpretation [of the association] is causation").

a. Motion to strike

As an initial matter, the Court must resolve Pfizer's Motion to Strike the March 6, 2008, Affidavit of McGwin. In the affidavit, McGwin stated that "the adjusted associations between Viagra and NAION and between Cialis and NAION were similar." (McGwin Aff. (Docket No. 427) at 1.) Plaintiffs claim to have submitted the affidavit in response to the Court's question at the hearing about what research was tailored to Viagra use as opposed to, for example, the PDE5 inhibitor Cialis.

Pfizer contended that the affidavit should be stricken because it is untimely, amends McGwin's sworn deposition testimony, prejudices Pfizer because it has no opportunity for cross-examination, and is unreliable because Plaintiffs failed to provide the underlying data. Plaintiffs characterize the affidavit as consistent with McGwin's deposition testimony and appropriate where as here the Court exercised its discretion in resolving the Daubert Motions without live testimony.

Although the Court does not endorse Plaintiffs' procedure for merely filing McGwin's additional affidavit without seeking leave first, the Court rejects Pfizer's contention that it is unduly prejudiced by this additional testimony. As discussed below, the Court has ordered that Pfizer be provided meaningful opportunity to cross-examine McGwin as to his report and conclusions, and questions as to the additional affidavit may be included during those examinations.

The Court's question regarding Viagra and Cialis is one that undoubtedly will arise during trials, and it is highly likely that Pfizer would have asked McGwin a question

substantially similar to the one that the Court asked. Under these circumstances, Pfizer's Motion to Strike is properly denied.

b. McGwin's report and deposition testimony

McGwin began his analysis by assessing the "strength of association" between Viagra and NAION. Regarding this association, McGwin stated that the McGwin et al. study reported an "odds ratio (OR) of 1.75 with a 95% confidence interval (CI) of 0.48 to 6.30." (McGwin Rep. at 2.) In other words,"the odds of Viagra use were 75% greater among men with NAION compared to age-matched controls." (Id.) The study further reported an OR of 10.7 for men who reported Viagra use and had a history of myocardial infarction, and an OR of 6.9 for Viagra users who had a history of hypertension. McGwin then cited the Margo et al. study, which involved the related disorder nonarteritic ischemic optic neuropathy ("NION"). That study reported an RR factor of 1.10 regarding exposure to PDE5 inhibitors. In other words, "men who were dispensed PDE-5 inhibitors were 10% more likely to have a diagnosis or possible diagnosis of NION compared to those who had not been dispensed these medications." (Id.)

McGwin then addressed the second Bradford Hill factor regarding consistency and asserted that it was satisfied because the McGwin et al. and Margo et al. studies were consistent with each other in that they collectively demonstrate "an overall increased risk level of between 10- and 75-percent" regarding Viagra use and NAION. (Id. at 3.)

Regarding temporality, McGwin stated that the McGwin et al. study suggested a causal relationship between Viagra use and NAION because "the authors only evaluated

Viagra use that occurred prior to [a] NAION diagnosis date," but that temporality could not be assessed in the Margo et al. study. (Id.) Regarding biologic plausibility, McGwin stated that Viagra's "mild systemic hypotensive" and possible "optic nerve fiber crowding" effects suggest that Viagra can cause NAION. (Id.)

McGwin did not meaningfully examine the specificity or dose-response factors. As for the remaining Bradford Hill factors, McGwin stated that the findings in his report are coherent with known facts of NAION, there have been no human clinical trials or animal experiments, and that case reports regarding PDE5 inhibitor ingestion and NAION satisfy the analogy factor.

Finally, McGwin critiqued the Gorkin study, which suggests that Viagra users are at no increased risk for developing NAION than is the general population. According to McGwin, the Gorkin study is unreliable because the sample size was too small and the data ill-suited for assessing a possible temporal relationship. (Id. at 4-5.)

In a deposition, McGwin confirmed that the odds ratio in the McGwin et al. study and the relative risk factor in the Margo & French study were not "statistically significant," and that the data in the Gorkin study indicate that NAION incidence in sildenafil users is "consistent with the range of estimated NAION incidence in the general U.S. population." (McGwin Dep. at 84-85, 106, 124-25.) Nevertheless, McGwin again stated his conclusion as being that "to a reasonable degree of scientific certainty, it is my opinion that Viagra can cause NAION and the other ocular vascular disorders." (Id. at 228.)

c. Analysis

Pfizer contends that McGwin's report is unreliable because it is not based on statistically significant data and fails to satisfy the Bradford Hill criteria. (Pfizer's Supp. Mem. at 18.) The Court agrees that the Bradford Hill criteria are helpful for determining reliability but rejects Pfizer's suggestion that any failure to satisfy those criteria provides independent grounds for granting its Daubert Motion. The key question is whether McGwin's report is unreliable because it is based on data that he concedes are not statistically significant.

Statistical significance is among the factors the Court should examine when determining reliability. See Daubert, 509 U.S. at 592 ("in the case of a particular scientific technique, the court ordinarily should consider the known or potential rate of error"); Gen. Elec. Co., 522 U.S. at 146-47 (court may exclude testimony regarding statistically insignificant scientific findings when the findings, "whether individually or in combination, [fail] to support their conclusions"); Glastetter, 252 F.3d at 990 (affirming exclusion of testimony where data "presented statistically insignificant results").

Because the CI in the McGwin et al. study "includes the number 1.0," it can be accepted that the study "show[s] no statistically significant association between the factor and the disease." Brock, 874 F.2d at 312. In addition, because the RR in the Margo et al. study is 1.10, there is authority indicating that the research fails to provide "reliable evidence of specific causation." Reference Manual at 349, 384 (citing Daubert II, 43 F.3d at 1321; Manko, 636 F. Supp. at 1438).

However, the inquiry at this stage involves general causation. (See Pfizer's Reply

Mem. at 12 (issue of specific causation "is not before the Court on this Motion").) Therefore, the authority suggesting that the RR value renders the Margo et al. study per se unreliable is distinguishable. See Miller, 196 F. Supp. 2d at 1079 (rejecting argument that evidence is admissible only if RR is greater than 2.0). There is persuasive authority stating that on a Daubert motion involving general-causation evidence in an MDL matter, lack of statistical significance under some circumstances "does not detract from the reliability of the study." In re Phenylpropanolamine (PPA) Prods. Liab. Litig., MDL No. 1407, 289 F. Supp. 2d 1230, 1241 (W.D. Wash. 2003).

Pfizer cites the Eighth Circuit Court of Appeals' decision in Glastetter, but in that situation, expert evidence was excluded because "rechallenge and dechallenge data" presented statistically insignificant results and because the data involved conditions "quite distinct" from the conditions at issue in the case. 252 F.3d at 990. Here, epidemiologic data is at issue and the studies' conditions are not distinct from the conditions present in the case. The Court does not find Glastetter to be controlling.

In this situation, the McGwin et al. and Margo et al. studies were peer-reviewed, published, contain known rates of error, and result from generally accepted epidemiologic research. The studies satisfy the precise standards that the Supreme Court has signaled that the Court should consider when determining reliability. Daubert, 509 U.S. at 592-95; compare Bickel v. Pfizer, Inc., 431 F. Supp. 2d 918, 923 (N.D. Ind. 2006) (excluding expert conclusion that Lipitor caused arteritic anterior ischemic optic neuropathy because of "failure to apply any scientific methodology" (emphasis added); In re Rezulin Prods. Liab. Litig., 369

F. Supp. 2d at 423 (excluding expert testimony where plaintiffs' theory "never has been tested and necessarily has no error rate"). The fact that the data appear not to result from post-litigation research further establishes its reliability for general-causation purposes on a Daubert Motion. Sappington, 512 F.3d at 449.

Further, the Gorkin research appears to directly contradict the McGwin et al. and Margo et al. research. Because "questions of conflicting evidence must be left for the jury's determination," the Court cannot conclude at this stage that McGwin's proffered testimony "is so fundamentally unsupported that it can offer no assistance to the jury [that] such testimony be excluded." In re Baycol Prods. Litig., 532 F. Supp. 2d at 1036 (citing Bonner, 259 F.3d at 929-30).

However, an additional comment is warranted. In this MDL matter, it is imperative that the transferor courts retain complete discretion over the ultimate admissibility of McGwin's report and testimony. Given the nature of the data underlying McGwin's report, Pfizer must be afforded meaningful opportunity for cross-examination in each individual case. See Bonner, 259 F.3d at 929 ("it is up to the opposing party to examine the factual basis for the opinion in cross-examination"). The Court can foresee how lack of such an opportunity would provide grounds for a transferor court to exclude the evidence. This discretion is particularly important to underscore where, as here, the claims and defenses involving causation appear to be issues of state law. See, e.g., In re Diet Drugs (Phentermine, Fenfluramine, Dexfenfluramine) Prods. Liab. Litig., MDL No. 1203, 2000 WL 876900, at *7 (E.D. Pa. June 20, 2000) (citing transferor courts' discretion to exclude

"preservation depositions" under Fed. R. Evid. 403 where "the state substantive law applied by these transferor courts may be different").

d. Conclusion

In conclusion, the Court denies Pfizer's Motion to Strike McGwin's affidavit and Pfizer's Daubert Motion as it relates to McGwin's report and proffered testimony. However, the Court directs that Pfizer must be afforded meaningful opportunity to cross-examine McGwin and reminds the parties that the ultimate determination as to admissibility of his testimony necessarily rests with the transferor courts.

2. Howard D. Pomeranz, M.D.

Plaintiffs' second expert, Howard D. Pomeranz, is a medical doctor and ophthalmologist whom Plaintiffs credit with co-authoring the first case report of someone who developed NAION after taking Viagra and also analyzed other such case reports. Plaintiffs seek to have Pomeranz testify about a possible temporal relationship between sildenafil use and NAION.

a. Pomeranz's report and deposition testimony

The first case in Pomeranz's report was of a "healthy 50 year-old man who had ED due to prostate cancer surgery." The man experienced 30 minutes of blurred vision an hour after ingesting sildenafil and the same symptoms the next night but without improvement. A medical exam revealed "visual field defect in the left eye and a swollen left optic disk, consistent with NAION." (Pomeranz Rep. at 4.) Pomeranz described the report as "challenge-rechallenge" data. See Glastetter, 252 F.3d at 990 ("Rechallenge occurs when

a doctor re-exposes a patient to a drug believed to have caused an earlier adverse reaction.").

In 2002, Pomeranz co-published "a summary of 5 patients with NAION associated with sildenafil use," which included the man involved in the first case report. (Pomeranz Rep. at 4.) According to Pomeranz's expert report:

> Four of these five patients had no identifiable vascular risk factors. All of the patients had the small cup-to-disk ratio associated with NAION. Four of the five patients reported vision loss within several hours after oral ingestion of sildenafil. Three of the patients developed NAION after using sildenafil the first time, either after one or two doses, or after using the medication for a few days. The other two patients had been using the medication periodically for 1-2 years.

(Id.)

In 2005, Pomeranz co-published a report documenting "an additional seven patients with NAION associated with sildenafil use. Six patients experienced vision loss within 24 hours after use of sildenafil. All affected men had pre-existing vascular disease." (Id. at 5.)

In his expert report, Pomeranz drew these conclusions:

> Compelling arguments for a cause-and-effect association between NAION and the ED drugs include the (1) temporal relationship between onset of ocular symptoms and drug ingestion that is well documented in the cases published in the peer-reviewed medical literature, (2) a suggestive challenge-rechallenge history also well documented in the peer-review medical literature, and (3) a biologically plausible mechanism of effect on arterial perfusion of the optic disk, described by [researcher Sohan Singh] Hayreh, a well-recognized authority on NAION.

(Id. at 6.)

At his deposition, Pomeranz further clarified that while he has not concluded that Viagra causes NAION, there is a temporal association between Viagra and NAION:

> QUESTION: Is it your hypothesis that Viagra can cause NAION?

> POMERANZ: No. At this time, I described in my papers that there's a temporal association between the two. And I've put forward possible hypotheses, but I don't purport to have a mechanistic answer to that. I think it's — because no one understands completely what the mechanism of NAION is, to incite something as being a specific cause without knowing all the pathophysiology that underlies a condition I think is difficult to do.

(Pomeranz Dep. at 152-53.)

b. Analysis

Case reports generally are less reliable than epidemiologic research. In re Rezulin Prods. Liab. Litig., 369 F. Supp. 2d at 406; Reference Manual at 475. Rechallenge data, while "substantially more valuable than run-of-the-mill case reports," are properly excluded when "the paucity of examples presented statistically insignificant results." Glastetter, 252 F.3d at 990-91. Reports of this type are subject to the general rule that "temporal association . . . is not scientifically valid proof of causation." Id. at 990. However, "[u]nder some circumstances, a strong temporal connection is powerful evidence of causation," such as when acute symptoms are seen "immediately after . . . exposure" to a substance. Bonner, 259 F.3d at 930-31 (citing Heller v. Shaw Indus., 167 F.3d 146, 154 (3d Cir. 1999) ("if a person were doused with chemical X and immediately thereafter developed symptom Y, the need for published literature showing a correlation between the two may be lessened")).

The Court concludes that Pomeranz's report—which provides a less-than-strong temporal association between sildenafil and Viagra, a single challenge-rechallenge case, and the Hayreh research—fails to provide appropriate validation to Pomeranz's conclusion that there are "compelling arguments for a cause-and-effect association between NAION and the ED drugs." (Pomeranz Rep. at 6.)

Pomeranz's report seems to focus on eleven men who experienced vision loss somewhere between several hours and twenty-four hours after using sildenafil. However, because a majority of them had "pre-existing vascular disease" or "identifiable vascular risk factors" (see Pomeranz Rep. at 4, 6), any cause-and-effect relationship between Viagra and NAION would be "subjective speculation." Glastetter, 252 F.3d at 989. As an MDL court made clear on a Daubert motion involving allegations that the diabetes drug Rezulin causes liver damage: "The difficulty with case reports . . . is distinguishing between association and causation. Simply because a patient exposed to a particular substance exhibited a set of symptoms does not mean that it was the substance that caused the symptoms." In re Rezulin Prods. Liab. Litig., 369 F. Supp. 2d at 406. The same difficulties are present here.

The fact that these men out of untold millions of sildenafil users developed NAION within a 24-hour period fails to evince an "immediate" reaction to a substance as was present in Bonner. 259 F.3d at 930-31. The lone rechallenge case appears to stand in isolation and is fairly characterized as a "paucity." See Glastetter, 252 F.3d at 991. This is not a situation where the "sheer volume of case reports, case series, and spontaneous reports" bolsters the reliability of non-epidemiologic research. In re Phenylpropanolamine (PPA) Prods. Liab. Litig., 289 F. Supp. 2d at 1242. To the degree that Pomeranz has incorporated Hayreh's research, the incorporation is either cumulative or unreliable given the Court's ruling as to Hayreh's testimony, discussed infra.

Plaintiffs offer Pomeranz as a general-causation expert to presumably establish that Viagra can cause NAION. However, when he was asked whether Viagra "can cause

NAION," his answer was "no." (Pomeranz Dep. at 152-53.) Therefore, his proffered testimony fails to provide a "valid . . . connection to the pertinent inquiry." See Kumho Tire Co., 526 U.S. at 149. Accordingly, the Court grants Pfizer's Daubert Motion as it relates to Pomeranz's testimony in its entirety.

3. Sohan Singh Hayreh, M.D.

Plaintiffs' third expert is Sohan Singh Hayreh, a medical doctor and ophthalmologist who has studied more than 1,000 people with NAION and is credited with giving the disorder its name. (Hayreh Dep. 308-09; Pls.' Opp'n Mem. at 34.) His report contains an overview of factors that influence the blood flow in the optic nerve head and explains the various risk factors for NAION. Hayreh's report further suggests that there is "a cause-and-effect relationship between erectile dysfunction drugs and development of NAION." (Hayreh Rep. at 5.) This suggestion is based on a "nocturnal hypotension" theory involving low blood pressure during sleep.

a. Hayreh's report

Hayreh's report begins by explaining the anatomy of the eye and optic nerve and then provides a specific but non-exhaustive list of eleven predisposing risk factors for NAION: "high blood pressure, diabetes, cardiovascular diseases, high cholesterol, atherosclerosis, arteriosclerosis, massive or recurrent bleeding, migraine, sleep apnea, defective autoregulation of the optic nerve head, narrowing of the blood vessels supplying the optic nerve head, and many more." (Hayreh Rep. at 4.)

Hayreh then identifies the "precipitating risk factors"—specifically, "that at least 73%

of patients with NAION gave a definite history of discovering the visual loss on waking up in the morning or from a nap, or early in the morning at the first opportunity to use critical vision." (Id.) His report then explains that blood pressure is lower during sleep and that drugs prescribed "for a variety of conditions, such as heart failure or other heart diseases, enlarged prostate, migraine, as well as for high blood pressure, similarly cause an abnormal drop of blood pressure during sleep." (Id.) The report goes on to explain that men who take Viagra are more likely to have high blood pressure, diabetes, and other "factors that make them vulnerable to NAION." (Id.)

Finally, the report suggests a "relationship between NAION and Viagra and other drugs used for erectile dysfunction." (Id. at 5.) According to Hayreh, because NAION most often is reported upon awakening in the morning and Viagra is most often taken at night or before bed, "[w]hen all the evidence is put together, it becomes evident that Viagra and other erectile dysfunction drugs can result in the development of NAION—not always and in everyone but in persons with predisposing risk factors." (Id.)

b. Analysis

Pfizer asks the Court to exclude Hayreh's testimony because his nocturnal hypotension theory as it relates to Viagra has not been tested or subjected to peer review and publication and is not generally accepted. Therefore, according to Pfizer, the theory does not satisfy Daubert's "non-exhaustive list of factors a district court should consider when performing its gatekeeper function." Sappington, 512 F.3d at 449. Plaintiffs contend that Hayreh's theory satisfies these factors as well as "additional factors, including, whether the

expertise was developed for litigation or naturally flowed from the expert's research; whether the proposed expert ruled out other alternative explanations; and whether the proposed expert sufficiently connected the proposed testimony with the facts of the case." Id.

The Court finds Hayreh's report helpful for explaining eye and optic nerve anatomy, NAION risk factors including factors related to blood pressure, and the effect of various drugs on blood pressure. Therefore, the Court denies Pfizer's Daubert Motion as it relates to Hayreh's testimony on these subjects (see Hayreh Rep. Parts I-II) because the testimony will assist the triers of fact with "understand[ing] the evidence." Fed. R. Evid. 702.

However, the Court finds that Hayreh's hypothesis regarding a purported "relationship between NAION and Viagra and other drugs used for erectile dysfunction" fails to satisfy most of the "non-exhaustive" as well as "additional" factors referenced above. Plaintiffs do not meaningfully dispute that Hayreh's specific theory has not been tested, but they contend that this fact is not controlling because "[t]he exact mechanism by which NAION occurs is not known." (Pls.' Opp'n Mem. at 36.) The fact that NAION's cause is not known does not explain whether Hayreh's theory can or cannot be tested. See Daubert, 509 U.S. at 591.

As for the publication and "general acceptance" factors, Plaintiffs state that Hayreh's theory "has been published in numerous peer-reviewed journals, including the prestigious Journal of Opthalmology [sic]." (Pls.' Opp'n Mem. at 38.) For support, Plaintiffs direct the Court to a footnote in an article and a "non-exhaustive list of journal articles citing to Dr. Hayreh's theory on nocturnal hypotension." (Exs. 26-27 (Docket No. 413).) These materials do not help the Court assess to what degree Hayreh's theory has been vetted in these journals

or whether that theory has been generally accepted among the medical community.

Regarding the Eighth Circuit's "additional factors," the fact that Hayreh's nocturnal hypotension theory appears not to result from this litigation weighs in favor of the theory's admissibility. See Sappington, 512 F.3d at 449. However, proffered testimony about the theory fails to satisfy the other factors. Instead of ruling out alternative explanations, see id., Hayreh essentially rules in eleven "predisposing risk factors" such as high-blood pressure and diabetes—risk factors that a substantial number of Viagra users, given their age, possess.

This case is not about nocturnal hypotension. It is about whether Viagra can and ultimately has caused NAION. In Daubert, the Supreme Court observed that although studying moon phases might help a trier of fact determine whether it was dark on a given night, evidence of a full moon does not "assist the trier of fact in determining whether an individual was unusually likely to have behaved irrationally on that night." Daubert, 509 U.S. at 591. Similarly, studying nocturnal hypotension might help a trier of fact determine what causes NAION, but Hayreh's theory does not adequately explain whether Viagra can cause NAION, and his testimony would not meaningfully assist a trier of fact with determining whether Viagra has caused NAION in the Plaintiffs. The theory is "[e]xpert testimony which does not relate to any issue in the case" and therefore "is not relevant, and, ergo, non-helpful." Id. at 591 (citation omitted). Rather, it would be confusing. In re Baycol Prods. Litig., 532 F. Supp. 2d at 1054 (excluding expert testimony where it would "cause jury confusion").

In conclusion, the Court grants Pfizer's Daubert Motion as it relates to Hayreh's

proffered testimony that Viagra and other erectile dysfunction drugs can result in development of NAION. However, the Court denies the Motion as it relates to Parts I and II of his expert report that relate to eye and optic nerve anatomy, NAION risk factors including blood pressure, and the fact that several drugs affect blood pressure.

4. Augustine S. Aruna

Plaintiffs' fourth expert is Augustine S. Aruna, who holds a doctorate in pharmacy degree and is a professor of clinical pharmacy at Xavier University. Plaintiffs seek to have Aruna testify that Viagra can be "ruled in" as a cause of NAION based on the "totality of the evidence," which, according to Plaintiffs, includes Aruna's "expertise in pharmacology, . . . the known pharmacologic properties of Viagra, his application of the universally accepted Naranjo probability test, case reports, peer-reviewed literature and textbooks, a biological plausible mechanism of action, and his differential diagnosis of [one] challenge-rechallenge case." (Pls.' Opp'n Mem. at 45.)

a. Aruna's report

Aruna's conclusion as expressed in his expert report is that "[s]ildenafil (Viagra) can cause NAION and other ocular disorders in patients who ingest the drug; and that Sildenafil (Viagra) can be a substantial contributing factor in the development of NAION, especially in patients who may have other risk factors." (Aruna Rep. at 2.) In support of that opinion, Aruna states that he found it "particularly helpful to discuss the case of Mr. James E. Thompson, who developed NAION following his ingestion of Sildenafil (Viagra)." According to Aruna, Mr. Thompson developed NAION within 24 hours of taking sildenafil

and "[o]ther potential and/or predisposing risk factors of NAION were ruled out in his case." (Id.) The report goes on to provide results from Mr. Thompson's "Naranjo Adverse Drug Reaction Probability Scale Score" to establish general causation. (Id. at 9.)

b. Analysis

Pfizer does not challenge Aruna's qualifications but instead seeks to have his testimony excluded because his case report on a single Viagra user's development of NAION is "scientifically invalid" for proving general causation. Even if Aruna is qualified to render an expert opinion on pharmacology or otherwise, the Court finds his expert report wholly inadequate for purposes of assisting a trier of fact with determining whether Viagra can be "ruled in" as a cause of NAION.

Aruna's reliance on a single case study and the inadequately explained "Naranjo" scale do not constitute "sufficient facts or data" for general causation. Glastetter v. Novartis Pharms. Corp., 107 F. Supp. 2d 1015, 1037 & n.21 (E.D. Mo. 2000) (case report involving one individual "is not sufficient to establish causation), aff'd, 252 F.3d 986 (8th Cir. 2001). A report that bases a conclusion that Viagra "can cause NAION" on a single case report that a pharmacologist finds "particularly helpful" is not "the product of reliable principles and methods" or a result of "intellectual rigor." See Fed. R. Evid. 702; Kumho Tire Co., 526 U.S. at 152 (1999). Rather, Aruna's conclusions resemble the "subjective speculation that masquerades as scientific knowledge" that the Eighth Circuit has held must be excluded under Daubert. Glastetter, 252 F.3d at 989. Accordingly, the Court grants Pfizer's Daubert Motion as it relates to Aruna's testimony.

C. Pfizer's Experts

1. Stephen Kimmel, M.D.

Pfizer's first expert is Stephen Kimmel, M.D., an associate professor of epidemiology at the University of Pennsylvania who has focused his research on unintended cardiac effects of noncardiac drugs. He also is an internist and cardiologist with a master's of science degree in clinical epidemiology.

In his report, Kimmel states that he has "reviewed the scientific literature of studies that have been performed," including the McGwin et al., Margo et al., and Gorkin studies that are discussed in McGwin's report. (Kimmel Rep. at 3.) Kimmel also critiques Aruna's report as well as FDA "adverse event reports" regarding sildenafil use. Kimmel's conclusion is as follows:

> [A]lthough case reports and spontaneous adverse event reporting raise the hypothesis that PDE5 inhibitors may increase the risk of NAION, comparative studies have not confirmed this hypothesis and the evidence does not support a causal relationship. There is thus no reliable scientific evidence to establish a causal association between PDE5 inhibitors and NAION.

(Id. at 31.)

Plaintiffs contend that Kimmel is unqualified to offer expert opinions on ophthalmology and NAION and that his testimony should be excluded as unreliable. However, "Rule 702 does not require a defense medical expert to be of the identical medical specialty as the plaintiff's expert." Robinson v. GEICO Gen. Ins. Co., 447 F.3d 1096, 1100 (8th Cir. 2006). "Gaps in an expert witness's qualifications or knowledge generally go to the weight of the witness's testimony, not its admissibility." Id. (internal quotation omitted).

The Court finds Kimmel qualified for purposes of assisting the trier of fact with determining whether medical research indicates that Viagra can cause NAION in the individual plaintiffs.

Plaintiffs further contend that Kimmel's testimony is unreliable because he relies on Pfizer-sponsored research, did not perform any research himself, and prepared his report only as part of this litigation. These claimed deficiencies are matters for cross-examination. See, e.g., Daubert II, 43 F.3d at 1319 (when report does not result from pre-litigation research, "experts must explain precisely how they went about reaching their conclusions and point to some objective source . . . to show that they have followed the scientific method").

Further, given the lack of statistical significance in the data cited in McGwin's report, it is imperative that Pfizer be provided means to present expert evidence to counter McGwin's testimony. See Daubert, 509 U.S. at 595 ("[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence"). Therefore, Plaintiffs' Motion to exclude Kimmel's testimony is denied. However, because the Court has granted Pfizer's Motion regarding Aruna's testimony, the Court observes that Kimmel's proffered testimony in response to Aruna's testimony is not necessary and likely should be excluded at trial.

2. Peter A. Netland, M.D., Ph.D.

Pfizer's second expert is Peter A. Netland, who has a Ph.D. degree from Harvard University in physiology and biophysics and a medical degree from the University of California, San Francisco. He is a glaucoma specialist and professor of ophthalmology at the University of Tennessee.

Netland cites Hayreh's hypothesis regarding nocturnal hypotension and summarizes the ten studies investigating sildenafil's effect on ocular circulation (four supported by Pfizer and six not) to conclude that "[e]vidence-based literature review shows excellent evidence for increase or no change of ocular blood flow after sildenafil administration, with no evidence in the literature of a harmful effect (decrease)." (Netland Rep. at 2.) Therefore, Netland states that "evidence is weak for the suggested association of sildenafil citrate use and non-arteritic anterior ischemic optic neuropathy (NAION), generally based upon case reports." (Id.)

Plaintiffs contend that because Netland is not a neurologist, he is not qualified to offer expert opinions regarding NAION. However, the Court finds his qualifications sufficient pursuant to the decision in Robinson, 447 F.3d at 1100, and also on par with Plaintiffs' expert Hayreh who is not a neurologist and whose testimony the Court has found admissible within the parameters described above.

Plaintiffs' chief complaint with Netland's report is his use of an "Evidence Based Medicine" ("EBM") analysis to assess merits of studies regarding sildenafil's effect on ocular circulation. According to Netland, "EBM categorizes different types of clinical

evidence and ranks them according to the strength of their freedom from the various biases that beset medical research. According to EBM, case reports are rated as weak evidence." (Netland Rep. at 14.) Plaintiffs, meanwhile, contend that EBM "minimizes the importance of case reports" and fails to recognize the source of evidence—specifically, that "numerous publications relined on by Dr. Netland for his EBM-based opinion were sponsored or written by Pfizer." (Id. at 26.)

Plaintiffs have cited no authority indicating that testimony based on an EBM analysis is unreliable under Daubert. Authority tends to suggest that an expert may rely on EBM. See In re Prempro Prods. Liab. Litig., Nos. 4:03-CV-1507 & 4:05-CV-163, 2006 WL 2414062, at *7 (E.D. Ark. Aug. 21, 2006) (ruling that expert was "clearly qualified to testify about evidence-based medicine"); Carhart v. Ashcroft, 331 F. Supp. 2d 805, 978 (D. Neb. 2004) ("[e]vidence-based medicine has, over the last two decades, become accepted in the medical community"), aff'd 413 F.3d 791 (8th Cir. 2005), rev'd on other grounds, 127 S. Ct. 1610 (2007).

Plaintiffs' criticism of Netland's EBM analysis goes to the "credibility of the testimony, not the admissibility." In re Baycol Prods. Litig., 532 F. Supp. 2d at 1036. Therefore, the Court denies Plaintiffs' Daubert Motion as it relates to Netland's testimony. However, to the degree Pfizer intends to use Netland's testimony to counter Hayreh's testimony, the use must be consistent with the parameters of Hayreh's testimony set forth above.

3. John W. Gamel, M.D.

Pfizer's third expert is John W. Gamel, a medical doctor, ophthalmologist, and professor emeritus at the University of Louisville School of Medicine's Department of Ophthalmology and Visual Sciences. He has focused his research on a specialty known as "medical retina" and has examined persons with optic-nerve disorders including NAION.

In his expert report, Gamel cites studies indicating that while "[c]linical trials have revealed a variety of visual symptoms in patients taking sildenafil," animal studies indicate that sildenafil makes no "structural change to any ocular tissue" and any visual symptoms are not permanent. (Gamel Rep. at 4-5.) In his report's conclusion, Gamel writes:

> Numerous animal studies and controlled clinical trials disclose no scientific evidence that PDE-5-inhibitors exert a permanent effect on the structure or function of the visual system. No study of ocular blood flow shows that these drugs diminish circulation within any tissue; in fact, some findings show that they enhance ocular blood flow, especially within the network of posterior ciliary arteries whose para-optic branches supply the optic nerve head (ONH). Since NAION is thought to result from ischemia of the ONH, this evidence mitigates strongly against the PDE-5-inhibitors playing a toxic role in the development of NAION.

(Id. at 21.)

Plaintiffs challenge Gamel's qualifications, but the Court finds Gamel sufficiently qualified pursuant to Robinson, 447 F.3d at 1100. Plaintiffs' chief complaint goes to the purported unreliability of the testimony—that Gamel ignored McGwin's work and the case reports suggesting a close temporal relationship between sildenafil use and NAION, and that he inordinately relied on animal studies. (Pls.' Supp. Mem. at 34, 36-37.)

However, given the Court's conclusions explained above regarding Plaintiffs'

proffered expert testimony on temporal relationships between sildenafil use and NAION, it would be improper to exclude Gamel's testimony on grounds that he failed to cite studies assessing any temporal relationship. It is true that courts should be cautious in presuming that findings derived from animal studies are applicable to humans. Gen. Elec. Co., 522 U.S. at 144-45. However, the applicability of animal studies can be explored during cross-examination. Accordingly, the Court denies Plaintiffs' Daubert Motion as it relates to Gamel's testimony.

CONCLUSION

The lack of statistical significance in data underlying McGwin's proffered testimony does not render the testimony unreliable under Daubert for purposes of general causation. However, it does require that Pfizer be given ample opportunity for cross-examination. See In re Baycol Prods. Litig., 532 F. Supp. 2d at 1036 ("[a]lthough it is common that medical experts often disagree on diagnosis and causation, questions of conflicting evidence must be left for the jury's determination").

In addition, Hayreh's testimony as to eye and optic nerve anatomy, NAION risk factors including those associated with blood pressure, and the several drugs that affect low-blood pressure will assist the triers of fact with understanding the evidence and ultimately determining whether Viagra can and in fact has caused NAION in each Plaintiff.

However, because Plaintiffs have failed to meet their burden for establishing the reliability of the other expert testimony, it must be excluded pursuant to Daubert. Pfizer, meanwhile, has met its burden in response to Plaintiffs' Daubert Motion and necessarily must

be provided means to offer expert testimony in response to Plaintiffs' expert testimony. Accordingly, **IT IS HEREBY ORDERED** that:

1. Pfizer's Motion to Exclude Plaintiffs' Experts (Docket No. 387) is **GRANTED in part** and **DENIED in part**;
2. Plaintiffs' Motion to Exclude Pfizer's Generic Causation Experts (Docket No. 390) is **DENIED**; and
3. Pfizer's Motion to Strike the March 6, 2008, Affidavit of Gerald McGwin, Jr. (Docket No. 428) is **DENIED**.

Dated: April 2, 2008

s/ Paul A. Magnuson
Paul A. Magnuson
United States District Court Judge